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Soluble Guanylate Cyclase α_1 -Deficient Mice: a novel murine model for Primary Open Angle Glaucoma

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Background

Glaucoma is an optic neuropathy characterized by retinal ganglion cell degeneration leading to vision loss. Primary open angle glaucoma is a subtype of glaucoma that results in visual field loss due to optic nerve damage caused by increase in intraocular pressure. Events in primary open angle glaucoma (POAG) pathogenesis has been associated with nitric oxide (NO) which activates the soluble guanylate cyclase (sGC), a heterodimeric enzyme consisting of α and β subunits by c GMP signaling.^{1,2} In POAG patients NO metabolites and level of c GMP has been found to be decreased in aqueous humor. Impaired signaling can be a contributing risk factor to the etiology of the POAG.³ However whether signal impairment can result in POAG and mechanism underlying is yet to be elucidated.

In the present work authors have identified a novel murine model to study the pathogenesis of age related optic neuropathy in POAG. Further study was extended to human subjects to explore the role of sGC in POAG pathophysiology in case of humans by performing gene association studies.

Study Design

1 to 17 months old mice deficient in sGC α_1 and age matched wild type mice were studied for POAG disease development. Female mice were studied to rule out the systemic hypertension that may give confounding effects. To determine the localization of sGC α_1 and β_1 subunits immunohistochemical studies were carried in mice retinal sections as well as sections of human eyes obtained from New England Eye Bank. sGC α_1 and sGC β_1 were found to be expressed abundantly at three major site ciliary muscles, smooth muscles of retinal vessels and retinal ganglion cells. The expression in these sites suggested that sGC might change contractibility of ciliary muscles, regulates blood flow or viability of RGC that ultimately lead to the disease. Retinal damage in young and old sGC α_1 mice as compared to age matched wild

type was assessed by measuring retinal nerve fibre layer (RNFL) and retinal thickness using non invasive technique of Spectral domain-optical coherence tomography. Retinal thinning was observed in old sGC α_1 mice when compared with age matched WT mice but not in age matched young sGC and WT mice. Longitudinal studies were performed to investigate the impact of deficiency of sGC α_1 on intraocular pressure. Central Corneal thickness (CCT) and depth of anterior chamber (DAC) were other parameters analyzed. DAC was measured using in-vivo ultrasound biomicroscopy. No significant difference was found in CCT. When intraocular pressure (IOP) was measured which is one of the major risk factor of POAG again elevated pressure was observed in sGC β_1 old mice comparable to age matched WT.

Fluorometric technique was utilized to assess the outflow rate of aqueous humor which revealed that 57 week old sGC α_1 mice has less aqueous humor clearance than the same aged WT. Vascular dysfunction in retina was analyzed by measuring retinal arterial diameter by *in-vivo* laser ophthalmoscopy. Further to explore the role of sGC in human POAG, association between POAG and genes encoding α and β subunits of sGC was studied by single nucleotide polymorphism analysis in individuals with the disease.

Implications

The present study has demonstrated that deficiency of sGC α_1 leads to primary open angle glaucoma in old mice and thus sGC α_1 mice provide a valuable tool for translational studies for POAG. This novel animal model may further be explored to deduce the mechanism or signal transduction leading to POAG. Genetic analysis studies revealed the relevance of this mouse model in case of humans. It can also be concluded from the present study that sGC is a potential target enzyme to be exploited for POAG therapeutics.

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References

1. Nimmegeers S, Sips P, Buys E, et al. Functional role of the soluble guanylyl cyclase alpha(1) subunit in vascular smooth muscle relaxation. *Cardiovasc Res.* 2007; 76: 149–159.
2. Friebe A, Mergia E, Dangel O, et al. Fatal gastrointestinal obstruction and hypertension in mice lacking nitric oxidesensitive guanylyl cyclase. *Proc Natl Acad Sci U S A.* 2007; 104: 7699–7704.
3. Galassi F, Renieri G, Sodi A, et al. Nitric oxide proxies and ocular perfusion pressure in primary open angle glaucoma. *Br J Ophthalmol.* 2007; 88: 757–760.